Chapter 8

Summary

SUMMARY OF THIS THESIS

Chapter 1 outlines the scope of this thesis. Hypertensive disorders of pregnancy affect 3-10% of all pregnancies. Presentations vary from chronic hypertension, to gestational hypertension and preeclampsia (hypertension and proteinuria or other systemic symptoms). Hypertensive disease may, when it progresses, result in serious complications for the mother such as HELLP syndrome, eclampsia, placental abruption, organ failure and even death. In addition, it is associated with neonatal complications such as growth restriction, preterm birth and intra-uterine demise.

The only definitive treatment is delivery of the placenta. The management of hypertensive disorders remains a clinical dilemma: the benefits of earlier delivery for the mother (to prevent progression of the disease) have to be weighed against the consequences of a preterm delivery for the neonate. At term, beyond 37 weeks, immediate delivery reduces maternal complications without harming the neonate. Before term this balance is more complicated. **Part 1** of this thesis provides insight in optimal timing of delivery in non-severe late preterm hypertensive disorders regarding both short and long-term outcomes.

Screening and prevention of hypertensive disorders are current topics to improve maternal and fetal outcomes. A recent large randomized controlled trial showed that in women at high risk for preeclampsia 150mg of aspirin before 16 weeks of gestation reduces the rate of early and preterm preeclampsia. Therefore, identification of women at high risk to prevent early and preterm preeclampsia by administration of aspirin is important. The FMF preeclampsia screening algorithm has shown promising results, but feasibility outside the algorithm development setting needs to be evaluated prior to implementation in the Netherlands. In addition, implementation requires high risk cut-off values for a certain population. **Part 2** of this thesis focusses on first trimester prediction of preeclampsia in the Netherlands.

Part 1: Timing of delivery for optimal management in late preterm hypertensive disorders

The HYPITAT II trial randomized women with hypertensive disorders of pregnancy between 34 and 37 weeks of gestation to immediate delivery or expectant monitoring. Immediate delivery did reduce adverse maternal outcomes (1.1% vs 3.1%; relative risk (RR) 0.36, 95% CI 0.12–1.11), but it significantly increased

respiratory distress syndrome (5.7% vs. 1.7%; RR 3.3, 95% CI 1.4–8.2). Although expectant monitoring remained the preferred management, based on these short-term outcomes, long-term consequences of obstetric management in offspring of women with hypertensive disorders in preterm pregnancy are largely unknown.

Chapter 2 reports on the two year follow-up of the HYPITAT II trial. The effects of immediate delivery versus expectant monitoring on neurodevelopmental and behavioral outcomes at two years of age were compared in offspring of women with mild late preterm hypertensive disorders. Participating women from the HYPITAT II were asked to complete the Ages and Stages Questionnaire (ASQ) for developmental outcome and the Child Behavior Checklist (CBCL) for behavioral problems when their toddlers were two years old. These validated questionnaires are proven to be adequate to screen for developmental delays and behavior problems. The ASQ and CBCL outcomes were compared between the two randomization groups. We received 330 questionnaires (61% of the approached group). In the immediate delivery group, 28% (n=45/162) of the infants had an abnormal ASQ-score compared to 18% (n=27/148) in the expectant monitoring group (risk difference 9.6%; 95% CI 0.3% to 18.0%; p = 0.045). In the pregnancies (n=94) that delivered before reaching 36 weeks, 27% (n=25) had an abnormal ASQ score compared to 22% (n=47) when delivered after 36 weeks (OR 0.77 CI 0.44 – 1.34;). An abnormal CBCL outcome was found in 18% (n=31/175) in the delivery group versus 15% (n=24/166) in the expectant monitoring group (risk difference 3.2%; 95% CI -4.6% to 11.0%; p = 0.41). After correction for maternal education, management strategy remained an independent predictor of abnormal ASQ-score (OR 0.48, CI 0.24 -0.96). In multivariable analyses, low birth weight, low maternal education and immediate delivery policy were all significantly associated with an abnormal ASQ-score. In this two year follow up study of the HYPITAT II trial we found that early delivery in women with late preterm hypertensive disorders is associated with poorer neurodevelopmental outcome of their children compared to expectant monitoring. These findings indicate an increased risk of developmental delay after management that indicated early delivery. This follow up study underlines the conclusion of the original HYPITAT II study that, until the clinical situation deteriorates, expectant monitoring remains the most appropriate management strategy in light of short- and long-term neonatal outcomes for hypertensive disorders in the preterm period.

Chapter 3 reports on the five year follow-up of the HYPITAT II trial. Neurodevelopmental and behavioral outcomes were compared between the two randomization groups. Five years after the original study 322 (46%) women were contacted for follow-up, of whom 148 (46%) responded. In the early delivery group 22% (n=14/65) of the children had an abnormal ASQ score compared to 21% (n=13/62) in the expectant monitoring group (risk difference 0.5%, 95% CI -13.7 to 14.7, p=0.94). Abnormal CBCL-scores were found in 19% (n=14/72) of the children in the delivery group versus in 27% (n=20/75) in the expectant monitoring group (risk difference 7.3%, 95% CI -20.9 to 6.3, p=0.30). The main predictor of development and behavior at 2 and 5 years was fetal growth restriction (for abnormal development OR 2.1, CI 1.0 – 4.4; for behavior problems OR 2.2, CI 1.1-5.5). Higher maternal education decreased abnormal behavior outcomes (OR 0.5, CI 0.2 - 0.9) and a similar tendency was observed for developmental problems (OR 0.6, CI 0.3 – 1.1). In addition, abnormal outcomes at the age of 2 are significant predictors of abnormal outcomes at the age of five: for ASQ OR 5.5 (95%CI 1.7-17.9) and CBCL OR 4.8 (95%CI 1.6-14.9). We concluded that in this five year follow up study we found no significant difference in developmental and behavioral outcome between the two management groups (immediate delivery vs. expectant monitoring). The increased risk of developmental delay after immediate delivery, that we found in the two year follow up study, did not persist at five years of age. Taking into account this long term follow up at two time points of the HYPITAT II trial, the conclusion remains: in preterm hypertensive disorders delivery should be deferred until the clinical situation justifies early delivery.

However, expectant monitoring might not be the best management strategy for all. Delivery might be beneficial in subgroups of women with high risk of clinical deterioration. Clinicians might need support to identify which women and/or neonates might benefit from earlier delivery.

In **chapter 4** we report on a model we developed to distinguish women at high risk from women at low risk of progression to severe disease. Maternal complications may be reduced if women at high risk could be identified and targeted for delivery. At the same time this may prevent unnecessary preterm births in women at low risk. The aim of the study was to identify predictors of progression to severe disease, which resulted in an indication for delivery. Women from the expectant arm of the HYPITAT II trial were included. Risk characteristics were measured at disease onset. Univariate and multivariate

logistic regression analysis were used to identify relevant variables from clinical and laboratory parameters. The performance of the resulting prediction model was assessed by ROC analysis, calibration and bootstrapping, using the average predicted probabilities.

We included 519 women of whom 115 (22.2%) developed severe hypertension that required delivery. The prediction model included: maternal age (OR 0.92 per year), gestational age (OR 0.87 per week), systolic blood pressure (OR 1.05 per mmHg), the presence of chronic hypertension (OR 2.4), platelet count (OR 0.996), creatinine (OR 1.02) and lactate dehydrogenase (OR 1.003). The model showed good fit (p = 0.64), fair discrimination (AUC 0.76, 95%CI 0.73 – 0.81, p < 0.001) and could stratify women in three risk groups of average, intermediate and high risk (predicted probabilities < 0.22, < 0.44 and > 0.45 respectively).

We concluded that, in women with a hypertensive disorder between 34 and 37 weeks of gestation, progression to severe disease can be predicted with this model. After external validation, this model could be applied to identify women at high risk and target them for delivery. In addition, women at intermediate risk could be monitored more frequently. This model has the potential to guide doctors in management of the individual women and prevent unnecessary interventions and progression to severe disease.

In **Chapter 5** we evaluated all available evidence regarding adverse outcomes by comparing immediate delivery vs. expectant monitoring in hypertensive disorders beyond 34 weeks of gestation. For this comparison we collected individual participant data of all available randomized controlled trials (HYPITAT I, HYPITAT II, DIGITAT, GRIT and Deliver or Deliberate). We followed the PRISMA-IPD guideline and utilized a 2-stage meta-analysis approach. Primary maternal outcome was a composite of HELLP syndrome and eclampsia and the primary neonatal outcome was respiratory distress syndrome (RDS). Primary outcomes were available for 1724 women. Immediate delivery reduced the composite risk of HELLP syndrome and eclampsia in all women (0.8% vs. 2.8%; RR 0.33, CI 0.15–0.73; I^2=0%; NNT 51, 95% CI 31.1–139.3). RDS risk increased after immediate delivery (3.4% vs. 1.6%; RR 1.94, CI 1.05–3.6; I^2=24%; NNH 58, 95% CI 31.1–363.1). Subgroups with a priori higher risk of HELLP and eclampsia might benefit from earlier delivery. Immediate delivery did reduce HELLP and eclampsia risk in women with preeclampsia (1.1% vs. 3.5%; RR 0.39, 95% CI 0.15–0.98), nulliparous women (1.0% vs. 3.4%; RR 0.29, 95% CI 0.12-0.71) and women with a higher cervical

length (0.6% vs 3.5%; RR 0.20, 95% CI 0.05-0.75). Infants born after randomization to immediate delivery at 35 weeks were at higher risk of RDS (5.1% vs. 0.6%; RR 5.5, 95% CI 1.0–29.6). RDS risk was lower in the 36th week, and did not reach statistical significance (1.5% vs. 0.4%; RR 3.4, 95% CI 0.4–30.3). Beyond 37 weeks RDS risk decreased (0.6% vs. 0.8%; RR 0.7, 95% CI 0.16 – 3.11) and management did not matter anymore. We concluded that immediate delivery reduces the risk of maternal complications, while the effect on the neonate depends on gestational age. In general, optimal timing of delivery would be at 37 weeks, but could be considered at 36 weeks in women with risk factors such as preeclampsia.

Part 2: Early screening for prevention of preeclampsia

In **Chapter 6** we evaluated the performance of the first trimester Fetal Medicine Foundation algorithm for the prediction of preeclampsia in the Netherlands. This was a prospective cohort study in which we screened nulliparous women and women with preeclampsia or intra-uterine growth restriction in previous pregnancy at 11-13 weeks of gestation. The risk of preeclampsia was calculated using the variables in the FMF algorithm: maternal characteristics and medical history, blood pressure, pregnancy associated plasma protein A (PAPP-A) and placental growth factor (PlGF), crown rump length and uterine artery pulsatility index. Performance of the model was evaluated by area under the ROC curves (AUC) and calibration at various gestational ages; based on the ROC curves optimal predicted risk cut-off values for our study population could be defined. The primary outcome was preeclampsia and gestational age at delivery. We analyzed 362 women, of whom 22(6%) developed preeclampsia. Five (1.4%) delivered before 34 weeks and 10 (2.8%) delivered before 37 weeks. The algorithm showed fair discriminative performance for PE <34 weeks (AUC 0.81; 95%CI 0.65-0.96). The model showed moderate discriminative performance for both preeclampsia <37 weeks (AUC 0.71; 95%CI 0.51-0.90) and <42 weeks (AUC 0.71; 95% CI 0.61-0.81). Optimal cut-offs based on our study population for PE<34, <37 and <42 weeks were 1:250, 1:64 and 1:22, respectively. Sensitivity and specificity based on these cut-offs were 80% and 80% for PE <34 weeks, 70% and 80% for PE <37 weeks and 68% and 68% for preeclampsia <42 weeks, respectively. Calibration was poor. The model underestimated lower probabilities and overestimated higher probabilities. In conclusion, the algorithm performance was satisfactory for early and preterm preeclampsia and less sufficient for late preeclampsia. We were able to identify optimal cut-off values for women at high risk of preeclampsia in our study population, for aspirin prophylaxis. Our results suggest that preeclampsia screening in the Netherlands is feasible, although

the reasons for sub-optimal performance of the screening should be addressed before successful implementation into clinical practice.

In **chapter 7** we assessed the quality of the uterine artery Doppler measurement. The uterine artery Doppler is one of the strongest predictors of preeclampsia in the FMF screenings algorithm. We evaluated the intra-observer and inter-observer reproducibility and generalizability for both the transabdominal and transvaginal route. We assessed whether maternal BMI and acquisition modality (transabdominal or transvaginal) affect feasibility and reliability of uterine artery Doppler measurement. The intra-observer and inter-observer reliability and generalizability was assessed by Lin's Concordance Correlation Coefficient (CCC) and intra-class correlation coefficient (ICC), a coefficient of 1 is perfect correlation. Agreement was expressed in Limits of Agreement (LoA), indicating 95% of the differences between the measurements limits of agreement closer to zero are optimal. This reproducibility study was performed in 101 women of the cohort described in **chapter 6**. Intra-observer reproducibility of the most experienced operator was ICC 0.87 for the transabdominal measurement LoA (-0.69; 0.64) and ICC 0.94 for the transvaginal measurement LoA (-0.51; 0.57). Inter-observer reproducibility was transabdominal ICC 0.92 LoA(-0.4;0.5) and transvaginal ICC 0.92 LoA (-0.52 ; 0.55) for the two experienced operators (2 to 6 year experience with the uterine artery Doppler) and lower with one less experienced operator (6 months), ICC 0.79 for transabdominal and ICC 0.74 for transvaginal with LoA (-0.96 ; 0.74) and (-1.22 ; 1.14) respectively. The uterine artery pulsatility index values did not differ significantly between the transabdominal or transvaginal approach. We were not able to demonstrate a correlation between BMI and time to obtain the transabdominal or transvaginal measurements (spearman's coefficient 0.83, p=0.44), or between BMI and transabdominal or transvaginal reproducibility (spearman's coefficient 0.87, p = 0.27). However, in four cases operators could not obtain the transabdominal measurement due to high BMI. We concluded that the uterine artery Doppler has moderate intra- and inter-observer reproducibility and agreement when measured by experienced operators.

Overall conclusion of **chapter 6 and 7** was that preeclampsia screening in the Netherlands is accurate, although future research should focus on cost-effectiveness. Further standardization of the uterine artery pulsatility index measurement and training should improve screening performance during implementation into clinical practice.